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The comparison of life compatibility between trisomy 2 and trisomy 21 (Down syndrome) by bioinformatic-based databases

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ABSTRACT

Objectives: Trisomy occurs with an extra chromosome during cell division resulting in 47 chromosomes instead of 46 in the human genome. The overexpression of gene profiles is associated with abnormal phenotypes and a range of syndromes. Theoretically, trisomy can occur for each chromosome but the survival rate of individuals with trisomy 21 is much higher than other trisomies. In this paper, we discussed the life compatibility of trisomy 21 compared to an example trisomy of one of the other chromosomes (chromosome 2) with quantitative and qualitative gene profiles using bioinformatic databases.

Methods: The analyses included (i) the determination of total gene numbers and classifications, (ii) numbers and functions of housekeeping genes, tissue-specific genes, and imprinted gene numbers and (iii) comparing the profiles of the proteins involved in cell survival and cell death in both chromosomes.

Results: The results indicate that trisomy 2 is likely to be incompatible with life compared to trisomy 21 because both gene enrichment and function are important factors associated with the difference in survival rates. Protein-protein interaction analyses showed that the increased interaction rate in trisomy 2 leads to more complex pathological consequences due to disruptions in cellular functions, however the limited interaction network in trisomy 21 may help explain the clinical features of Down syndrome.

Conclusions: Compared to trisomy 2, the life compatibility of trisomy 21 is associated with gene numbers, functions, and protein-protein interactions.

Keywords: Trisomy, Down syndrome, bioinformatics, chromosomal disorders, genetic disorders

Diploid organisms have two copies for each chromosome derived from individual parents (23 pair chromosomes in Homo sapiens). Homologous chromosomes segregate in meiosis during gametogenesis to form haploid sperms and oocytes. This segregation provides half a set of chromosomes which are then completed with another half set of chromosomes coming from another parent in fertilization. Meiosis maintains the number of chromosomes during transgenerational inheritance as well as provides genetic variations between generations by a special mechanism, crossing-over. If homologous chromosomes do not separate equally during meiosis, one of the gametes has a second copy of a chromo-

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some (n+1), and the other daughter gamete lacks a copy of chromosome (n-1) (Fig. 1). When such the n+1 gamete is fertilized and an embryo is formed, the resulting embryo contains an extra copy of that chromosome. The syndrome with three copies of a chromosome is called trisomy. If the n-1 gamete is fertilized, the embryo will have monosomy defined as a loss of a copy of a chromosome.

Trisomy 21 (also called Down syndrome) is the most common. Individuals with Down syndrome have multiple malformations, medical conditions, and cognitive impairment due to the presence of extra genetic material on chromosome 21 [1]. Although people with Down syndrome can have systemic syndromes that reduce life quality, they can still have a normal life as possible. This study aimed to reveal the molecular and genetic aspects of why the survival rate of individuals with Trisomy 21 is much higher than other trisomies, such as Trisomy 2. For this purpose, methods were considered to analyze gene groups both qualitatively and quantitatively. Bioinformatic databases were used to determine (i) total gene numbers in Chromosomes 2 and 21, (ii) the number and functions of housekeeping genes, tissue-specific genes, and imprinted genes, (iii) the profiles of the proteins involved in cell survival and cell death, and iv) the comparison of protein-protein interactions in Chromosomes 2 and 21. This study contributes to our understanding of how molecular differences between the two types of trisomies relate to the biological processes behind the phenotypic differences.

METHODS

Determination of Total Gene Numbers and Profiles

Gene numbers in the Chromosomes 21 and 2 were analyzed with the information obtained from the chromosome statistics tables in the Ensembl database by https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=21%3A1-1000 and https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=2%3A1-1000, respectively.

Databases Used for the Determination of Gene Groups

Housekeeping Genes

Housekeeping genes were obtained from the article "Human housekeeping genes are compact", compiled from https://www.tau.ac.il/~elieis/Housekeeping_genes.html [2], [3]. Housekeeping genes in chromosomes 2 and 21 were compiled from https://www.ncbi.nlm.nih.gov/

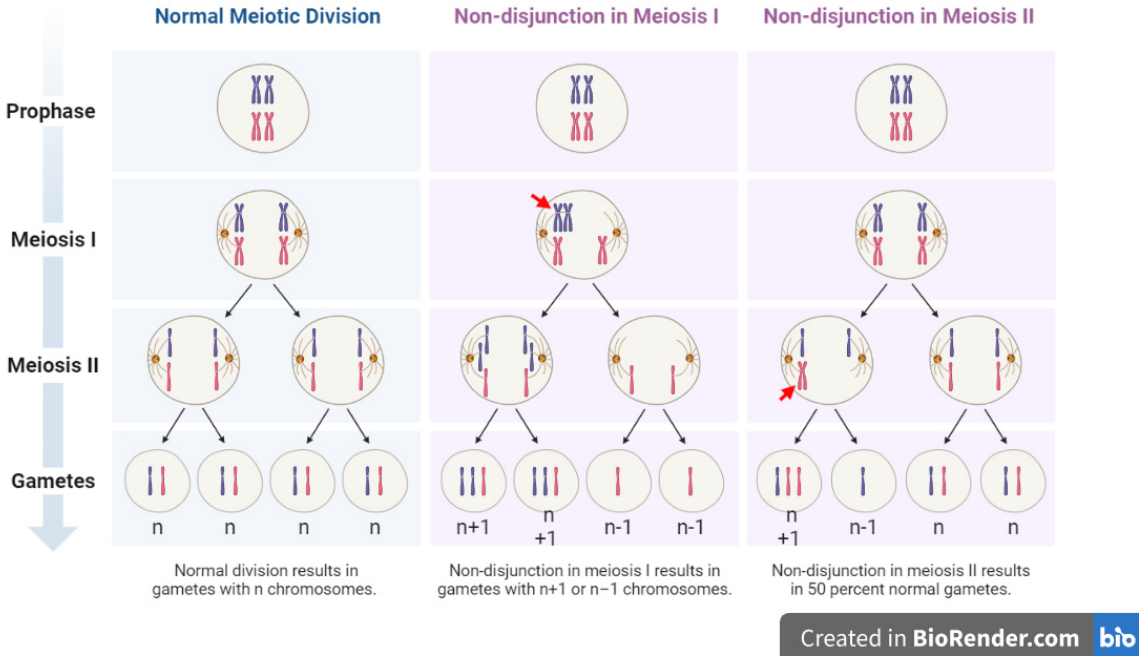


Fig. 1. Normal and abnormal gametogenesis. Non-disjunction can occur either in meiosis I or meiosis II. Both result in trisomy with a total of 47 chromosomes.

via Gene IDs to be classified to explain the chromosome, its position on the chromosome, NCBI gene identity, gene name, and function of the gene.

Imprinted Genes

Imprinted genes were screened from https://www.geneimprint.com/site/genes-by-species.Homo+sapiens for their presence on chromosomes 2 and 21. The imprinted genes are described with their chromosomal location, NCBI gene identity, gene name, maternal/paternal expression status, and tissue specificity.

Survival Proteins

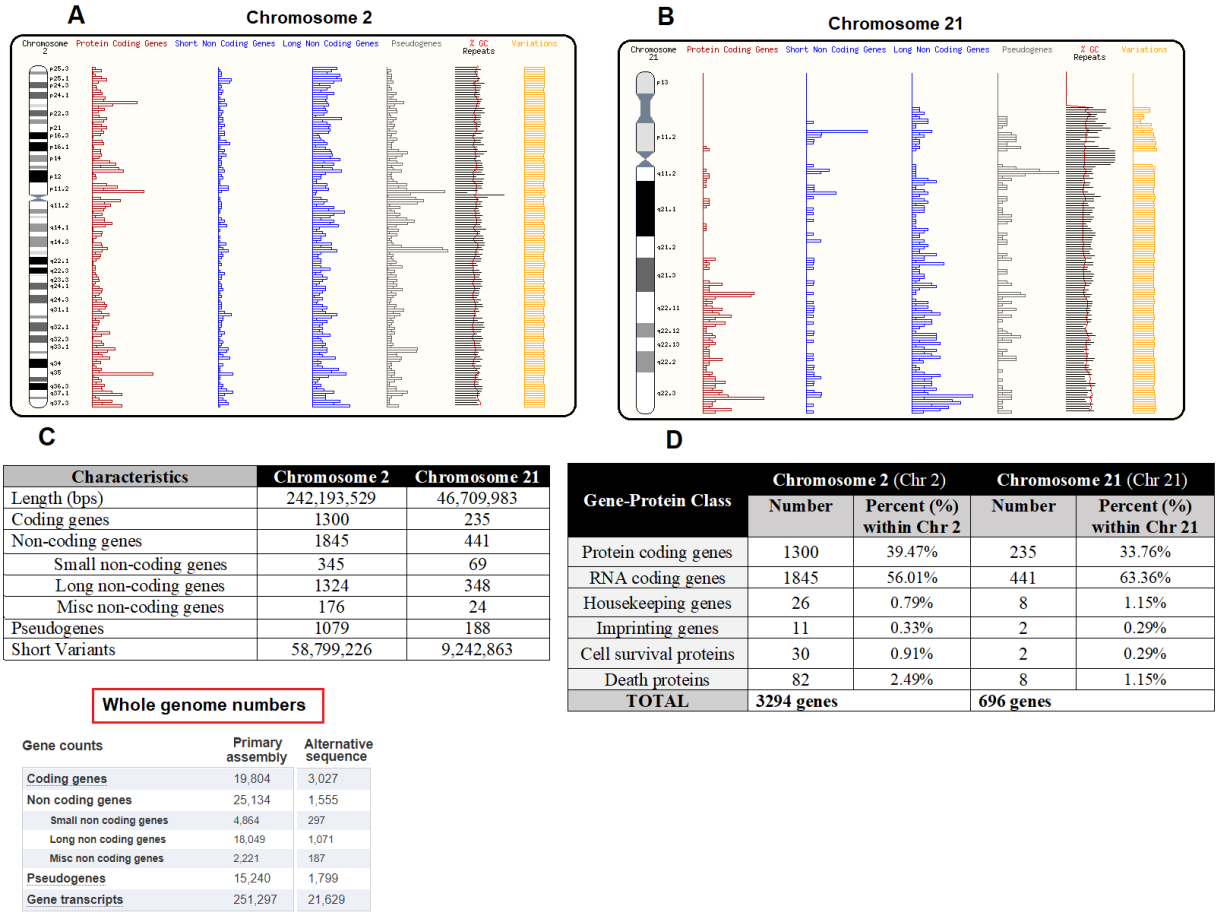
Profiles of the proteins involved in cell survival in chromosomes 2 and 21 of Homo sapiens were screened with the ontology number GO:0008283 from the AmiGO 2 database (http://amigo.geneontology.org/amigo) under the title of "cell proliferation" and analyzing 583 proteins.

Death Proteins

Profiles of the proteins involved in cell death in chromosomes 2 and 21 of Homo sapiens were screened with the ontology number GO:0008219 from the AmiGO 2 database (http://amigo.geneontology.org/amigo) under the title of "cell death" and analyzing 1735 proteins.

Protein-Protein Interaction Network Analysis with STRING Database

In this study, genes involved in processes such as genetic imprinting, cell survival, and cell death were selected to examine biological processes associated with trisomy 2 and trisomy 21. Genes were identified using Ensembl (https://www.ensembl.org), GeneImprint (https://www.geneimprint.com) and AmiGO 2 databases; especially Survival proteins and Death proteins data were extracted from AmiGO 2. Interaction networks of proteins encoded by selected genes were analyzed using STRING (Search Tool for the Retrieval



Characteristics	Chromosome 2	Chromosome 21
Length (bps)	242,193,529	46,709,983
Coding genes	1300	235
Non-coding genes	1845	441
Small non-coding genes	345	69
Long non-coding genes	1324	348
Misc non-coding genes	176	24
Pseudogenes	1079	188
Short Variants	58,799,226	9,242,863

Gene counts	Primary assembly	Alternative sequence
Coding genes	19,804	3,027
Non coding genes	25,134	1,555
Small non coding genes	4,864	297
Long non coding genes	18,049	1,071
Misc non coding genes	2,221	187
Pseudogenes	15,240	1,799
Gene transcripts	251,297	21,629

Gene-Protein Class	Chromosome 2 (Chr 2)		Chromosome 21 (Chr 21)	
	Number	Percent (%) within Chr 2	Number	Percent (%) within Chr 21
Protein coding genes	1300	39.47%	235	33.76%
RNA coding genes	1845	56.01%	441	63.36%
Housekeeping genes	26	0.79%	8	1.15%
Imprinting genes	11	0.33%	2	0.29%
Cell survival proteins	30	0.91%	2	0.29%
Death proteins	82	2.49%	8	1.15%
TOTAL	**3294 genes**		**696 genes**	

Fig. 2. Grouping of gene numbers in chromosomes 2 and 21. A and B show chromosomal maps for Chr2 and Chr21, respectively. C shows the genomic context of each chromosome, and D shows the comparison of gene-protein classes between Chr2 and Chr21.

of Interacting Genes/Proteins) database. STRING is a widely used bioinformatics tool to visualize protein-protein interactions and examine interaction densities. This database contains only interactions with high confidence levels that are confirmed by experimental evidence. The interaction networks of genes associated with trisomy 2 and trisomy 21 were examined separately to compare the protein interaction densities on chromosomes 2 and 21 in both cases. The effect of the extra chromosome on protein expression in trisomy 2 and the effect of chromosome 21 on protein interaction capacity in trisomy 21 were evaluated. Finally, the obtained interaction networks were visualized and comparisons were made between the interaction densities. In these analyses, interactions between survival and death proteins were particularly emphasized. Since the study was based solely on open-access biological databases, ethical committee approval was not required.

RESULTS

Chromosome 2 is the second largest human chromosome, representing almost 8% of the total DNA in human cells. It is 242,193,529 base pairs long including 1,300 coding genes. It has also 1,845 non-coding genes; of these, 345 are small noncoding genes, 1,324 are long noncoding genes, and 176 are other noncoding genes. It contains 1,079 pseudogenes and has 58,799,226 short variants (Figs. 2A and C). But chromosome 21 is 46,709,983 base pairs long including 235 protein-coding, and 441 non-protein-coding genes; 69 of these are small noncoding genes, 348 are long noncoding genes, and 24 are other noncoding genes. It also contains 188 pseudogenes and has 9,242,863 short variants (Figs. 2B and C). Chromosome 2 contains more than 6-fold coding genes and more than 4-fold non-coding genes than chromosome 21. Additionally, chromosomes 21 and 2 composed

Table 1. Housekeeping genes located on the Chr 2.

Location	NCBI Gene ID	Gene	Name	Overexpression	Function
2p16.1	6233	RPS27A	Ribosomal protein S27a, mRNA	Ovary, lymph node	Encodes a fusion protein consisting of ubiquitin at the N terminus and ribosomal protein S27a at the C terminus.
2p21	9167	COX7A2L	Cytochrome c oxidase subunit 7A2 like, mRNA; nuclear gene for mitochondrial product	Adrenal, kidney	Nuclear gene encodes a protein similar to polypeptides 1 and 2 of subunit VIIa in the C-terminal region
2p23.3	3030	HADHA	Hydroxyacyl-coa dehydrogenase trifunctional multi-enzyme complex subunit alpha, mRNA; nuclear gene for mitochondrial product	Duodenum, small intestine	Encodes the alpha subunit of the mitochondrial trifunctional protein, which catalyses the last three steps of mitochondrial beta-oxidation of long chain fatty acids.
2p14	5861	RAB1A	Member RAS oncogene family, mRNA	Kidney, thyroid	Encodes a member of the Ras superfamily of GTPases.
2q11.2	1329	COX5B	Cytochrome c oxidase subunit 5B, mRNA; nuclear gene for mitochondrial product	Colon, kidney	Encodes the nuclear-encoded subunit Vb of the human mitochondrial respiratory chain enzyme.
2p25.1	4953	ODC1	Ornithine decarboxylase 1, mRNA	Testis, bone marrow	Encodes the rate-limiting enzyme of the polyamine biosynthesis pathway which catalyses ornithine to putrescine.
2q14.1	7849	PAX8	Paired box 8, mRNA	Thyroid, kidney	Encodes a member of the paired box (PAX) family of transcription factors.
2q37.3	4735	SEPTIN2	Septin 2, mRNA	Fat, thyroid	Enables identical protein binding activity. Predicted to be involved in several processes, including cilium assembly; regulation of exocytosis; and smoothened signalling pathway.
2q37.1	5757	PTMA	Prothymosin alpha, mRNA	Bone marrow, lymph node	Enables DNA-binding transcription factor binding activity. Involved in negative regulation of apoptotic process.
2p13.3	6637	SNRPG	Small nuclear ribonucleoprotein polypeptide G, mRNA	Colon, appendix	The protein encoded by this gene is a component of the U1, U2, U4, and U5 small nuclear ribonucleoprotein complexes, precursors of the spliceosome.
2p21	805	CALM2	Calmodulin 2, mRNA	Brain, testis	Calmodulin is a calcium binding protein that plays a role in signalling pathways, cell cycle progression and proliferation. This gene is a member of the calmodulin gene family.

Table 1 contunied. Housekeeping genes located on the Chr 2.

Location	NCBI Gene ID	Gene	Name	Overexpression	Function
2p25.1	3241	HPCAL1	Hippocalcin like 1, mRNA	Lung, small intestine	The protein encoded by this gene is a member of neuron-specific calcium-binding proteins family found in the retina and brain.
2p23.3	3032	HADHB	Hydroxyacyl-CoA dehydrogenase trifunctional multi-enzyme complex subunit beta, mRNA; nuclear gene for mitochondrial product	Heart, duodenum	This gene encodes the beta subunit of the mitochondrial trifunctional protein, which catalyses the last three steps of mitochondrial beta-oxidation of long chain fatty acids.
2q31.1	518	ATP5MC3	ATP synthase membrane subunit c locus 3, mRNA; nuclear gene for mitochondrial product	Heart, duodenum	Encodes a subunit of mitochondrial ATP synthase. This gene is one of three genes that encode subunit c of the proton channel.
2q35	10109	ARPC2	Actin related protein 2/3 complex subunit 2, mRNA	Lymph node, bone marrow	The Arp2/3 protein complex has been implicated in the control of actin polymerization in cells and has been conserved through evolution. Encodes one of seven subunits of the human Arp2/3 protein complex.
2q11.2	56910	STARD7	StAR related lipid transfer domain containing 7, mRNA; nuclear gene for mitochondrial product	Kidney, brain	Predicted to enable lipid binding activity.
2p14	10438	C1D	C1D nuclear receptor corepressor, mRNA	Bone marrow, adrenal	The protein encoded by this gene is a DNA binding and apoptosis-inducing protein and is localized in the nucleus.
2q35	23549	DNPEP	Aspartyl aminopeptidase, mRNA	Small intestine, duodenum	The protein encoded by this gene is an aminopeptidase which prefers acidic amino acids, and specifically favours aspartic acid over glutamic acid.
2q35	27013	CNPPD1	Cyclin Pas1/PHO80 domain containing 1, mRNA	Kidney, adrenal	Predicted to be involved in regulation of cyclin-dependent protein serine/threonine kinase activity.
2p11.2	9168	TMSB10	Thymosin beta 10, mRNA	Appendix, colon	Predicted to be involved in regulation of cell migration and sequestering of actin monomers.
2p13.2	10574	CCT7	Chaperonin containing TCP1 subunit 7, mRNA	Testis, adrenal	Encodes a molecular chaperone that is a member of the chaperonin containing TCP1 complex (CCT), also known as the TCP1 ring complex (TRiC).
2p16.1	57142	RTN4	Reticulon 4, mRNA	Fat, brain	Reticulons are associated with the endoplasmic reticulum and are involved in neuroendocrine secretion or in membrane trafficking in neuroendocrine cells. This gene belongs to the family of reticulon encoding genes.
2q37.1	4691	NCL	Nucleolin, mRNA	Lymph node, appendix	Nucleolin (NCL), a eukaryotic nucleolar phosphoprotein, is involved in the synthesis and maturation of ribosomes. The intron 11 of the NCL gene encodes a small nucleolar RNA, termed U20.
2p15	4190	MDH1	Malate dehydrogenase 1, mRNA	Heart, fat	This gene encodes an enzyme that catalyses the NAD/NADH-dependent, reversible oxidation of malate to oxaloacetate in many metabolic pathways, including the citric acid cycle.
2p25.1	10971	YWHAQ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein theta, mRNA	Brain, endometrium	This gene product belongs to the 14-3-3 family of proteins which mediate signal transduction by binding to phosphoserine-containing proteins
2p13.3	113419	TEX261	Testis expressed 261, mRNA	Thyroid, testis	Predicted to be involved in endoplasmic reticulum to Golgi vesicle-mediated transport.

0.93% and 5% of the total coding genes in the human genome.

Chromosomes 21 and 2 differ in terms of gene functions. For instance, housekeeping gene content is higher in Chr2 than in Chr21 (Tables 1 and 2). The range of organs affected by selectively overexpressed housekeeping is wide in Chr2 compared to Chr21. Chromosome 21 has only 2 known imprinted genes, but Chromosome 2 has 11 imprinted genes (Table 3). Some of these genes are supposed to be imprinted (SI) with current knowledge. Interestingly all the two imprinted genes in Chr21 are of paternal origin and in-

Table 2. Housekeeping genes located on the Chr 21.

Location	NCBI Gene ID	Gene	Name	Overexpression	Function
21q22.3	1476	CSTB	Cystatin B, mRNA	Oesophagus, urinary bladder	Play a role in protecting against the proteases leaking from lysosomes.
21q22.3	8209	GATD3	Glutamine aminotransferase class 1 domain containing 3, mRNA; nuclear gene for mitochondrial product	Kidney, heart	This gene encodes a potential mitochondrial protein that is a member of the DJ-1/PfpI gene family. This protein is overexpressed in foetal DS brain.
21q22.3	1291	COL6A1	Collagen type VI alpha 1 chain, mRNA	Placenta, endometrium	The collagens are a superfamily of proteins that play a role in maintaining the integrity of various tissues. Collagens are extracellular matrix proteins. Collagen VI is a major structural component of microfibrils.
21q22.3	754	PTTG1IP	PTTG1 interacting protein, mRNA	Placenta, gall bladder	Induces transcriptional activation of basic fibroblast growth factor.
21q22.3	8888	MCM3AP	Mini chromosome maintenance complex component 3 associated protein, mRNA	Lymph node, spleen	One of the MCM proteins essential for the initiation of DNA replication.
21q22.11	6647	SOD1	Superoxide dismutase 1, mRNA	Liver, kidney	The protein encoded by this gene binds copper and zinc ions and is one of two isozymes responsible for destroying free superoxide radicals in the body.
21q22.11	539	ATP5PO	ATP synthase peripheral stalk subunit OSCP, mRNA; nuclear gene for mitochondrial product	Heart, duodenum	F-type ATPases are composed of a catalytic core and a membrane proton channel. The protein encoded by this gene is a component of the F-type ATPase found in the mitochondrial matrix.
21q22.3	**6612**	**SUMO3**	**Small ubiquitin like modifier 3, mRNA**	**Brain, bone marrow**	**This gene encodes a member of the small ubiquitin-related modifier (SUMO) family of eukaryotic proteins.**

Table 3. Comparison of imprinting gene profiles

Location	Gene	NCBI Gene ID	Status	Expressed allele	Tissue Specificity	Function
Chromosome 21						
21q22.2	SIM2	6493	Suppose to be imprinted (SI)	Paternal	Kidney, oesophagus, prostate gland	Encodes a transcription factor that is the master regulator of neurogenesis
21q22.2	DSCAM	1826	Imprinted (I)	Paternal	Brain	This gene is a member of the immunoglobulin superfamily of cell adhesion molecules (Ig-CAMs) and is involved in human central and peripheral nervous system development.
Chromosome 2						
2p12	LRRTM1	347730	I	Paternal	Brain, salivary gland, thyroid	Predicted to be involved in regulation of postsynaptic density assembly and regulation of presynapse assembly.
2p13	OTX1	5013	SI	Maternal	Skin, prostate gland, brain	This gene encodes a member of the bicoid sub-family of homeodomain-containing transcription factors. The encoded protein acts as a transcription factor and may play a role in brain and sensory organ development.
2p13	VAX2	25806	SI	Maternal	Brain	This gene encodes a homeobox protein and is almost exclusively expressed in the ventral portion of the retina during development.
2p16.1	CCDC85A	114800	SI	Paternal	Fat, brain, thyroid, placenta, lung	Located in adherens junction.
2p21	ABCG8	64241	SI	Maternal	Small intestine, duodenum, liver	ABC proteins transport various molecules across extra- and intra-cellular membranes. The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters.
2p21	CYP1B1	1545	SI	Paternal	Prostate, endometrium, appendix	The cytochrome P450 proteins are monooxygenases which catalyse many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Encodes a member of the cytochrome P450 superfamily of enzymes.
2p22.3-p21	ZFP36L2	678	SI	Maternal	Thyroid, appendix and other tissue	Regulating the response to growth factors.

Table 3 contunied. Comparison of imprinting gene profiles

Location	Gene	NCBI Gene ID	Status	Expressed allele	Tissue Specificity	Function
2q33.3	GPR1 (CMKLR2)	2825	I	Paternal	Placenta, oesophagus. skin	Enables adipokinetic hormone binding activity and adipokinetic hormone receptor activity.
2q33.3	ZDBF2	57683	I	Paternal	Adrenal, brain, ovary, thyroid	This gene encodes a protein containing DBF4-type zinc finger domains.
2q37.1	TIGD1	200765	SI	Paternal	Gene function is unknown	The protein encoded by this gene belongs to the tigger subfamily of the pogo superfamily of DNA-mediated transposons in humans.
2q37.3	MYEOV2 (COPS9)	150678	SI	Paternal	Brain, fat, kidney, prostate gland	Involved in several processes, including cellular response to UV; cytoplasmic sequestering of protein; and negative regulation of protein neddylation.

volved in nervous system development, while the nervous system-related imprinted gene ratio is around 1:3 within the group imprinted genes of Chr2. Imprinted genes with three alleles, as in trisomies, are problematic because the genome/cell cannot manage an extra paternal allele to be imprinted or not. Therefore, this extra allele may lead to chaotic gene expression. However, the chaos depends on the parental origin of the extra allele (within the extra Chr21). If an extra chromosome (and extra paternal allele) is provided by the paternal genome, this is supposed to be significant in a clinical manner.

We then assessed the profiles of genes involved in cell survival or cell death which might be directly related to life compatibility. 30 and 2 cell survival genes are found in Chr2 (Table 4) and Chr21 (Table 5), respectively. 82 and 8 cell death genes are found in Chr2 (Table 6) and Chr21 (Table 7), respectively. Chr2 con-

Table 4. Proteins involved in cell survival located on the Chr 2.

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	Q9NPC8	SIX2	Developmental protein, DNA binding	Morphogenesis
2	O95393	BMP10	Cytokine, developmental protein, growth factor	Cell adhesion
2	P98164	LRP2	Receptor	Endocytosis, hearing, neurogenesis, transport
2	Q12884	FAP	Hydrolase, protease, serine protease	Angiogenesis, apoptosis, cell adhesion
2	P02461	COL3A1	Matrix structural component molecule and ion binding	Morphogenesis
2	P20264	POU3F3	Developmental protein, DNA biding	Neurogenesis, transcription, transcription regulation
2	Q96SQ7	ATOH8	Developmental protein, DNA biding	Differentiation, neurogenesis, transcription, transcription regulation
2	P10809	HSPD1	Chaperone, isomerase	Host-virus interaction
2	P52951	GBX2	DNA binding	Transcription, transcription regulation
2	P24593	IGFBP5	Growth factor binding	Cellular response, aging
2	P62699	YPEL5	Metal binding	Cell proliferation
2	O95343	SIX3	Developmental protein, DNA binding, repressor	Transcription, transcription regulation
2	Q14623	IHH	Developmental protein, hydrolase, protease	Morphogenesis
2	P27037	ACVR2A	Kinase, receptor, serine/threonine-protein kinase, transferase	Cellular response
2	P42224	STAT1	Activator, DNA-binding	Antiviral defence, host-virus interaction, transcription, transcription regulation
2	Q8NER5	ACVR1C	Kinase, receptor, serine/threonine-protein kinase, transferase	Apoptosis
2	O43683	BUB1	Kinase, receptor, serine/threonine-protein kinase, transferase	Apoptosis, cell cycle, cell division, chromosome division, host-virus interaction, mitosis
2	P15336	ATF2	Activator, DNA-binding	DNA damage, transcription, transcription regulation
2	P35716	SOX11	Activator, developmental protein, DNA binding	Differentiation, neurogenesis, transcription, transcription regulation
2	P61026	RAB10	Hydrolase	Protein transport, transport

Table 4 contunied. Proteins involved in cell survival located on the Chr 2.

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	O14713	ITGB1BP1	Mitogen	Angiogenesis, biomineralization, cell adhesion, differentiation, Notch signaling pathway, transcription, transcription regulation
2	Q02363	ID2	Developmental protein, suppressor	Biological rhythms, transcription, transcription regulation
2	P13010	XRCC5	Activator, DNA binding, helicase, hydrolase	DNA damage, DNA recombination, DNA repair, host-virus interaction, immunity, innate immunity, ribosome biogenesis, transcription, transcription regulation
2	P23582	NPPC	Hormone, vasoactive	Osteogenesis
2	Q13873	BMPR2	Kinase, receptor, serine/threonine-protein kinase, transferase	ATP binder, magnesium, manganese, metal binder, nucleotide binder
2	P68106	FKBP1B	Isomerase, rotamase	Protein regulation
2	Q15118	PDK1	Kinase, transferase	Carbohydrate metabolism, glucose metabolism
2	Q8TAX0	OSR1	DNA binding, ion binding	Transcription, transcription regulation
2	P01135	TGFA	Growth factor, mitogen	Proliferation regulation
2	**P49279**	**SLC11A1**	**Transport**	**Ion transport**

tains the DNMT3A gene which encodes a de novo DNA methyltransferase playing an important role in embryo formation and epigenetic regulation. DNMT3A gene is considered a lethal gene as its loss or mutations deactivating its function cause embryo death and severe morphological defects. DNMT3A enzyme is critical to manage cell differentiation via regulating de novo DNA methylation of gene sets. This can lead to lower survival rates in the embryos with trisomy 2 compared to those with trisomy 21.

In this study, genes identified to be associated with biological processes such as genomic imprinting, cell survival, and cell death were selected. The interaction networks of the proteins encoded by these genes were also examined by bioinformatics analysis using the STRING database. In this analysis, specific to trisomy 2 and trisomy 21, important findings were obtained regarding the interaction densities and network structures of the proteins encoded by genes on Chr2 and Chr21.

In trisomy 2, the presence of an extra copy of chromosome 2 leads to higher expression levels of proteins encoded by Chr2, which increases the density of protein-protein interactions, leading to disruptions in biological processes during embryonic development (Fig. 3). This may help us understand the molecular mechanisms by which trisomy 2 often results in death at the embryonic stage.

In trisomy 21, the presence of an extra copy of Chr21 may lead to the overexpression of some proteins encoded by Chr21. However, the interaction capacities of these proteins remain low, especially in interactions with Chr2. This contributes to cellular abnormalities in the pathophysiology of DS and leads to a limited interaction network.

In addition, some proteins located on both Chr2 and Chr21 interact with each other (Fig. 4). These interactions suggest that proteins located on both chromosomes may be involved in common biological processes and may play important roles in regulating these processes. In particular, interactions between proteins encoded by Chr2 and Chr21 may play a critical role in maintaining a balance between cellular functions.

On the other hand, the proteins encoded by the genes on Chr21 that play a role in the biological processes we mentioned did not form any interaction networks according to the analyses we performed on

Table 5. Proteins involved in cell survival located on the Chr 21

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
21	Q01196	RUNX1	Activator, DNA-binding repressor	Transcription, transcription regulation
21	O95456	PSMG1	Chaperone	Proliferation regulator

Table 6. Proteins involved in cell death located on the Chr 2

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	Q9GZY8	MFF	Protein binding	Mitochondrial and peroxisomal fission
2	P10747	CD28	Protein binding	Apoptotic signaling pathway
2	O43683	BUB1	Protein kinase activity	Regulation of chromosome separation, apoptotic process
2	Q13467	FZD5	Ubiquitin protein ligase binding, Wnt-protein binding	Apoptotic process involved in morphogenesis
2	Q9BWT1	CDCA7	Transcriptional regulator	Apoptotic process
2	Q9BWP8	COLEC11	Developmental protein, DNA binding	Immunity, innate immunity
2	Q15303	ERBB4	Activator, developmental protein, kinase, receptor, transferase, tyrosine-protein kinase	Apoptosis, lactation, transcription, transcription regulation
2	Q0ZLH3	PJVK	Autophagy	Hearing
2	Q13901	C1D	DNA binding, repressor, RNA binding	Apoptosis, rRNA processing, transcription, transcription regulation
2	Q92835	INPP5D	Hydrolase	Apoptosis, immunity, lipid metabolism
2	Q92851	CASP10	Hydrolase, protease, thiol protease	Apoptosis
2	Q9HC96	CAPN10	Hydrolase, protease, thiol protease	Apoptosis and cellular response
2	Q13873	BMPR2	Kinase, receptor, serine/threonine-protein kinase, transferase	Morphogenesis and apoptosis
2	Q13618	CUL3	Cyclin binding, ubiquitin protein ligase activity	Cell cycle, cell division, cilium biogenesis/degradation, ER-Golgi transport, mitosis, Ubl conjugation pathway
2	Q658P3	STEAP3	Oxidoreductase	Apoptosis, cell cycle, ion transport, iron transport, transport
2	Q9NYY8	FASTKD2	RNA binding, rRNA binding	Apoptosis, mitochondrial ribosome biogenesis
2	Q01955	COL4A3	Extracellular structural component	Apoptosis, cell adhesion
2	O14901	KLF11	Activator, DNA-binding, repressor	Apoptosis, transcription, transcription regulation
2	Q8TEJ3	SH3RF3	Transferase	Apoptosis, Ubl conjugation pathway
2	P15408	FOSL2	DNA and chromatin binding	Cell death, transcription, regulation of transcription
2	P09529	INHBB	Cytokine, growth factor and hormone activity	Cellular response, regulation of apoptotic signalling pathway
2	P19447	ERCC3	DNA binding, helicase, hydrolase	Apoptosis, DNA damage, DNA repair, host-virus interaction, transcription, transcription regulation
2	Q9H8M9	EVA1A	Protein phosphorylation	Apoptosis, autophagy
2	A0PJW8	DAPL1	Connecting to the death domain	Apoptosis, differentiation
2	Q12884	FAP	Hydrolase, protease, serine protease	Angiogenesis, apoptosis, cell adhesion
2	Q9BST9	RTKN	GTP binding, GTPase inhibitory activity	Apoptosis
2	Q96Q42	ALS2	Guanine-nucleotide releasing factor	Cell death, transport
2	P56177	DLX1	Activator, developmental protein, DNA binding, repressor	Differentiation, transcription, transcription regulation
2	P09327	VIL1	Actin closure, actin binding	Apoptosis
2	Q15118	PDK1	Kinase, transferase	Carbohydrate metabolism, glucose metabolism
2	Q15116	PDCD1	An immune-inhibitory receptor	Adaptive immunity, apoptosis, immunity
2	Q8N5P1	ZC3H8	Repressor, RNA binder	Apoptosis, transcription, transcription regulation
2	Q96MX6	DNAAF10	Ubiquitin binding	Apoptosis
2	Q8NEG5	ZSWIM2	Transferase	Apoptosis, Ubl conjugation pathway
2	Q14790	CASP8	Hydrolase, protease, thiol protease	Apoptosis, host-virus interaction
2	Q9UBP9	GULP1	Adapter protein	Apoptosis, lipid transport, phagocytosis, transport
2	O95343	SIX3	Developmental protein, DNA binding, repressor	Transcription, transcription regulation
2	P52789	HK2	Allosteric enzyme, kinase, transferase	Apoptosis, glycolysis
2	P52701	MSH6	DNA and chromatin binding	DNA damage, DNA repair, host-virus interaction
2	Q569K4	ZNF385B	Nucleic acid, p53 and ion binding	Apoptosis
2	P62745	RHOB	Developmental protein	Angiogenesis, apoptosis, cell adhesion, differentiation, protein transport, transport
2	Q9Y2W7	KCNIP3	Ion channel, potassium channel, suppressor, voltage gated channel	Apoptosis, ion transport, potassium transport, transcription, transcription regulation, transport
2	Q9Y6K1	DNMT3A	Chromatin regulator, DNA binding, methyltransferase, repressor, transferase	DNA methylation, senescence, mitosis, apoptosis, genetic imprinting
2	O95630	STAMBP	Hydrolase, metalloprotease, protease	Ubl conjugation pathway
2	Q8NER5	ACVR1C	Kinase, receptor, serine/threonine-protein kinase, transferase	Apoptosis
2	P11234	RALB	Hydrolase	Apoptosis, cell cycle, cell division
2	P31483	TIA1	RNA binding	Apoptosis, mRNA processing, mRNA splicing

Table 6 contunied. Proteins involved in cell death located on the Chr 2

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
2	Q8IXB1	DNAJC10	Oxidoreductase, protein folding	Apoptosis
2	P21145	MAL	Lipid binding, participation in structure	Differentiation, central nervous system morphogenesis, apoptosis
2	O00506	STK25	Kinase, serine/threonine-protein kinase, transferase	ATP binder, magnesium, metal binder, nucleotide binder
2	P43354	NR4A2	DNA binding, receptor	Transcription, transcription regulation, differentiation, apoptosis
2	P06756	ITGAV	Host cell receptor, integrin, receptor for virus entry	Cell adhesion, host-virus interaction, apoptosis, angiogenesis
2	Q8TEB9	RHBDD1	Hydrolase, protease, serine protease	Apoptosis, differentiation, spermatogenesis
2	Q9Y2A7	NCKAP1	Regulates actin filament reorganization	Apoptosis, cell migration, cell morphogenesis, central nervous system development
2	Q9UNE0	EDAR	Developmental protein, receptor	Apoptosis, differentiation
2	P23760	PAX3	Developmental protein, DNA binding	Myogenesis, neurogenesis, transcription, transcription regulation
2	Q02156	PRKCE	Kinase, serine/threonine-protein kinase, transferase	Cell adhesion, cell cycle, cell division, immunity, apoptosis
2	Q99250	SCN2A	Ion channel, sodium channel, voltage gated channel	Ion transport, sodium transport, transport, memory, apoptosis
2	O94768	STK17B	Kinase, serine/threonine-protein kinase, transferase	Apoptosis, phosphorylation/autophosphorylation
2	O15519	CFLAR	Protease binding, endopeptidase activity	Apoptosis, cellular response, host-virus interaction
2	P61073	CXCR4	G-protein coupled receptor, host cell receptor for virus entry, receptor, transducer	Neurogenesis, morphogenesis, apoptosis, host-virus interaction
2	Q6NUQ4	TMEM214	Protein activation	Apoptosis
2	P28331	NDUFS1	Oxidoreductase, translocase	Electron transport, respiratory chain, transport, apoptosis
2	P43246	MSH2	DNA binding	DNA damage, DNA repair, apoptosis
2	Q8WYN3	CSRNP3	Activator, DNA-binding	Apoptosis, transcription, transcription regulation
2	Q8WYH8	ING5	Activator, chromatin regulator	Apoptosis, transcription, transcription regulation
2	P01584	IL1B	Cytokine, mitogen, pyrogen	Apoptosis, cell-cell signaling, reorganization of metabolic processes
2	P10809	HSPD1	Chaperone, isomerase	Host-virus interaction, apoptosis, protein folding
2	Q9Y3E7	CHMP3	Ubiquitin-specific protease binding, phosphatidylcholine binding	Apoptosis, cell cycle, cell division, protein transport, transport
2	Q16678	CYP1B1	Lyase, monooxygenase, oxidoreductase	Fatty acid metabolism, lipid metabolism, steroid metabolism, apoptosis, angiogenesis
2	Q9H2J4	PDCL3	Chaperone, VEGF receptor	Angiogenesis, apoptosis
2	O43464	HTRA2	Hydrolase, protease, serine protease	Apoptosis
2	Q9UMX3	BOK	Hydrolase, protease, serine protease	Apoptosis
2	Q9NP59	SLC40A1	Ion binding, hormone binding	Ion transport, iron transport, transport, apoptosis
2	Q9NPP4	NLRC4	ATP binding, caspase binding, ion binding	Apoptosis, immunity, inflammatory response, innate immunity
2	P15336	ATF2	Activator, DNA-binding	DNA damage, transcription, transcription regulation, apoptosis
2	P01583	IL1A	Cytokine, mitogen, pyrogen	Apoptosis, cell-cell signaling, reorganization of metabolic processes
2	O43521	BCL2L11	Microtubule binding, protein kinase binding	Apoptosis, morphogenesis
2	Q9NR63	CYP26B1	Monooxygenase, oxidoreductase	Lipid metabolism, cell fate determination, morphogenesis
2	Q9NR09	BIRC6	Protease inhibitor, thiol protease inhibitor, transferase	Apoptosis, cell cycle, cell division, mitosis, Ubl conjugation pathway
2	Q9NQC3	RTN4	RNA binding, ubiquitin protein ligase binding	Neurogenesis, apoptosis
2	**Q9NXR7**	**BABAM2**	**Chromatin organizer**	**Apoptosis, cell cycle, cell division, DNA damage, DNA repair, mitosis, Ubl conjugation pathway**

Table 7. Proteins involved in cell death located on the Chr 21

Chromosome	UniProtKB	Protein	Molecular Function	Biological Process
21	P58499	FAM3B	Cytokine	Apoptosis, glucose haemostasias
21	P20591	MX1	Protein and nucleotide binding	Antiviral defense, immunity, innate immunity
21	P00441	SOD1	Antioxidant, oxidoreductase	Cellular response, morphogenesis, apoptosis
21	Q14684	RRP1B	Activator	Apoptosis, host-virus interaction, mRNA splicing, transcription, transcriptional regulation
21	P055107	ITGB2	Integrin, receiver	Cell adhesion, phagocytosis, phagocytosis, apoptosis
21	P05067	APP	Heparin binder, protease inhibitor, serine protease inhibitor	Apoptosis, cell adhesion, endocytosis, Notch signaling pathway
21	P78563	ADARB1	Hydrolase, RNA binding	Antiviral defense, immunity, mRNA processing, morphogenesis
21	P57059	SIK1	Developmental protein, kinase, transferase	Biological rhythm, cell cycle, differentiation

the STRING database. This suggests that the proteins on Chr21 do not interact with each other and this deficiency may lead to more limited interaction networks in the pathophysiological processes of Down syndrome.

DISCUSSION

This study attempted to compare the life compatibility of trisomy 21 with trisomy 2 in terms of detailed gene profiles and protein-protein interactions. The total number of genes in the Chr21 is more than the Chr21 and the proteins encoded by Chr21 take part in more vital functions. On the other hand, the number of proteins involved in cell survival and cell death is higher in Chr2 compared with those in Chr21. In addition, it is remarkable that many of these proteins play a role in processes that affect the brain and form the nervous system, such as neurogenesis. The higher content of proteins involved in angiogenesis and other morphogenesis activities, cell and tissue differentiation, tran-

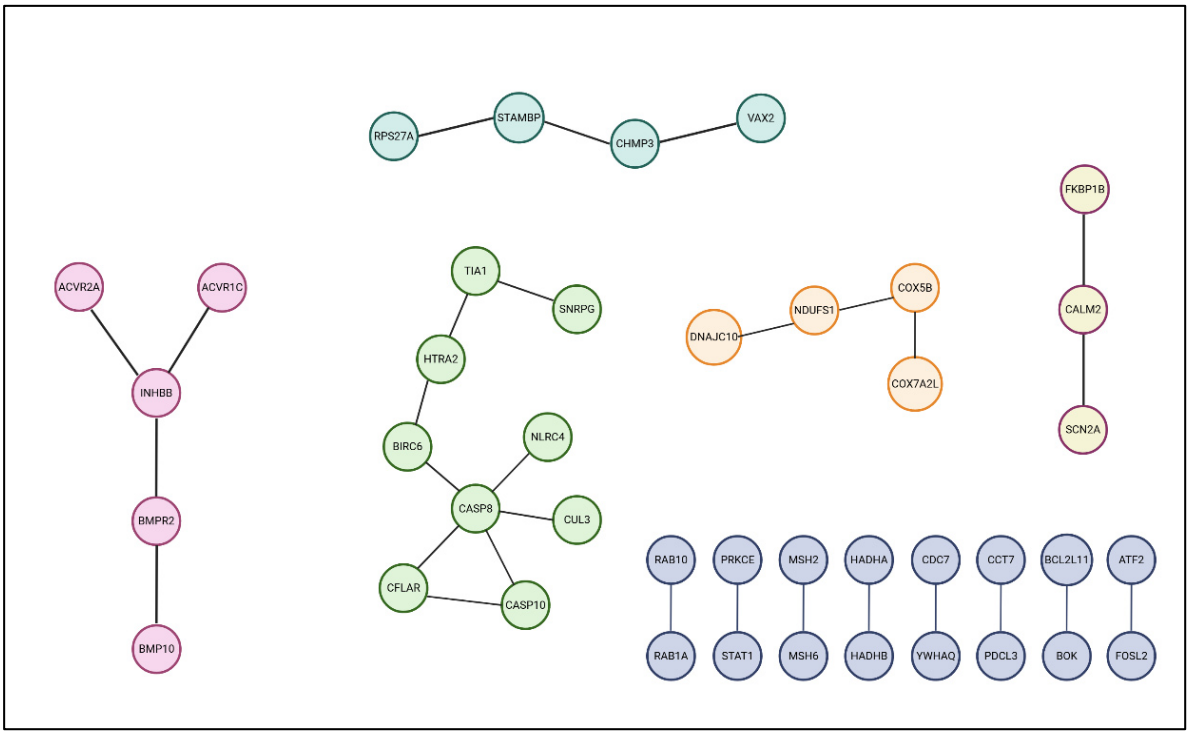


Fig. 3. The protein-protein interaction pathway of selected genes located on Chromosome 2, which are experimentally shown in the STRING database and identified as target proteins in our study. (The figures were created with BioRender program (https://app.biorender.com))

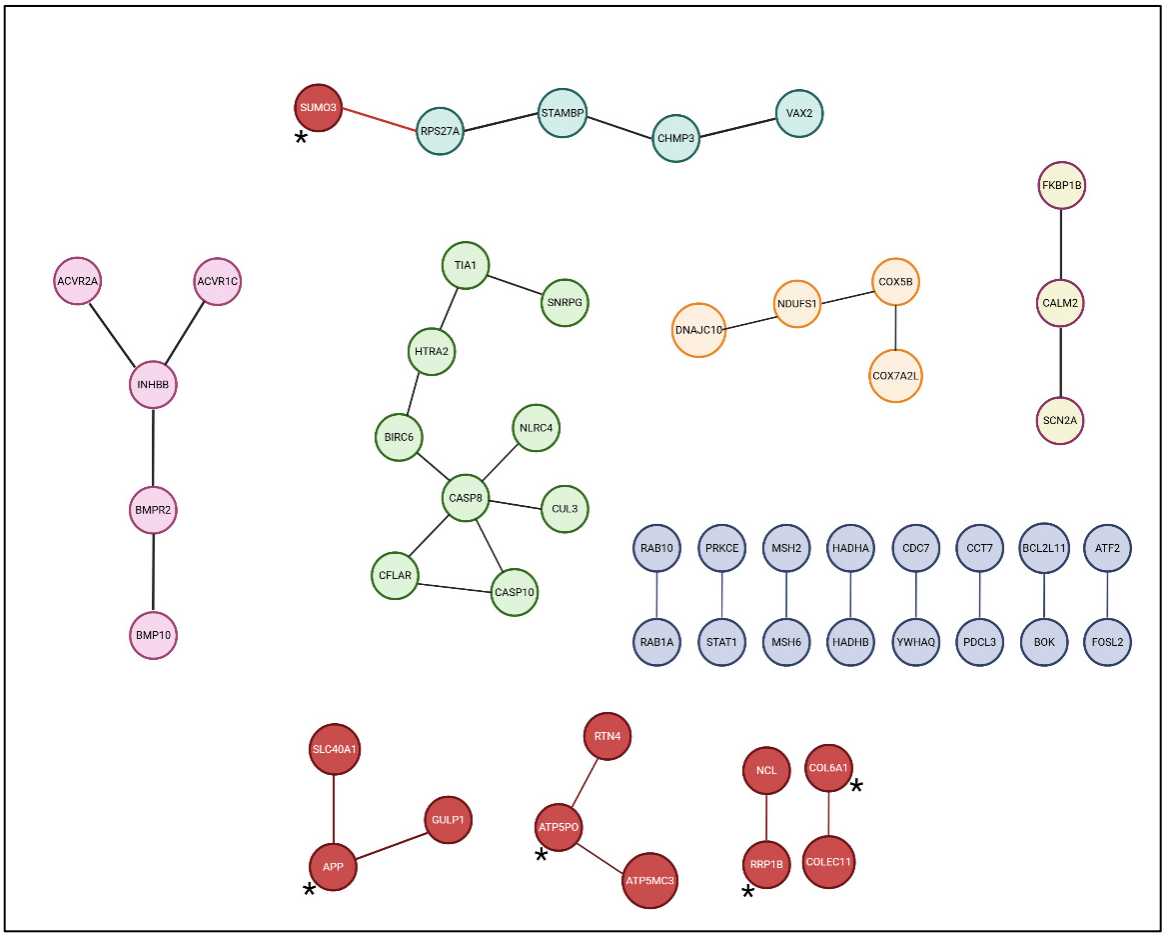


Fig. 4. The protein-protein interaction pathway of selected genes located on Chromosome 2 and 21, which are experimentally shown in the STRING database and identified as target proteins in our study. The protein interactions shown in red represent the interactions between selected genes located on Chromosomes 2 and 21. The proteins marked with an asterisk (*) are encoded by chromosome 21, while the remaining proteins are encoded by chromosome 2. (The figures were created with BioRender program (https://app.biorender.com))

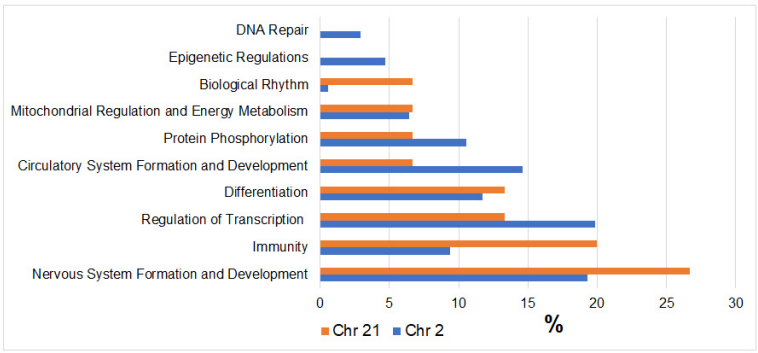
scription regulation, epigenetic regulation, biological rhythm, protein phosphorylation, energy metabolism, and DNA repair is observed in Chr2 compared to Chr21. These suggest that the life incompatibility of Chr2 compared to Ch21 can be explained if there are three copies of the same chromosome due to the gene dosage problem in many crucial cellular activities. Trisomy not only results in the up-regulation of genes but also leads to a genome-level transcriptomic dysregulation, whose downregulation affects each tissue and cell type differently because of epigenetic mechanisms and protein-protein interactions [4].

Aneuploidies are characterized by an extra copy of chromosomes resulting in three or more copies while monosomies are with a loss of chromosome resulting in a haploid chromosome. Diploid organisms have two copies of each gene localized within the homologous chromosomes and most of the genes have two-allele expression and some genes such as the X chromosome function as monoallelic expression. Therefore, gene dosage is an important aspect of the human genome. Aneuploidies are the abnormalities occurring with the distribution of cell dosage as well. However, not all defects in cell dosage may be incompatible with life. For instance, trisomy 21 is life-compatible compared to other trisomies and this should have a reason. Therefore, in this study, we tried to answer the possible reasons for this.

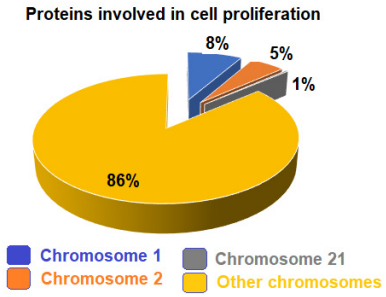
Life compatibility is a broad phenomenon, and the human genome is organized in different levels with high complexity. The molecular functions that are directly related cell survival or death should manage life

A

Cellular and Molecular Function	Chromosome 2 (Chr 2)		Chromosome 21 (Chr 21)	
	Number	Percent (%) within Chr 2	Number	Percent (%) within Chr 21
Nervous System Formation and Development	33	19.30%	4	26.67%
Regulation of Transcription	34	19.88%	2	13.33%
Mitochondrial Regulation and Energy Metabolism	11	6.43%	1	6.67%
Differentiation	20	11.70%	2	13.33%
Circulatory System Formation and Development	25	14.62%	1	6.67%
Immunity	16	9.36%	3	20.00%
Biological Rhythm	1	0.58%	1	6.67%
Epigenetic Regulations	8	4.68%	0	0.00%
Protein Phosphorylation	18	10.53%	1	6.67%
DNA Repair	5	2.92%	0	0.00%
TOTAL	**171 proteins**		**15 proteins**	



B



C

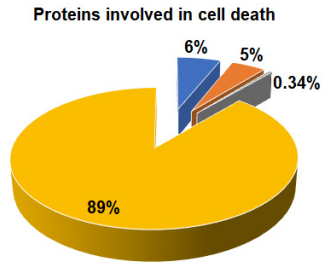


Fig. 5. Overview of proteins involved in cell death and cell proliferation. A shows the comparison of cellular and molecular functions of the genes between Chr2 and Chr21. B and C show the comparison of proteins involved in cell proliferation and cell death, respectively.

in the cells so that we focused on the proteins involved in these mechanisms. Cell survival and cell death related proteins are shown in 10 different molecular classes in Chr2 and Chr21 (This should be noted that some proteins were considered in more than one group) (Fig. 5A). In Chr2, almost 20% of genes are involved in nervous system development and 20% in transcription regulation followed by circulatory system formation (~15%), differentiation (~12%), protein phosphorylation (~11%), and immunity (~10%). Less than 1% of genes in Chr2 are involved in biological rhythm (Fig. 5A). Similarly, in Chr21 the major content is composed of nervous system development (~27% more than Chr2's content), but 20% of Chr21 is composed of immunity-related genes. The following are transcription regulation (13%), and differentiation (13%). Interestingly there is no gene involved in epigenetic regulation and DNA repair in Chr21, but ~5% and ~3% in Chr2 (Fig. 5A). Chr2 includes a gene coding a de novo DNA methyltransferase (DNMT3A) involved in epigenetic regulation which plays an important role in establishing methylation patterns during primitive germ cell development and early embryogenesis [5]. This indicates that it is a protein playing a crucial role in the formation of the embryo, in other words, it is responsible for determining its fate. Therefore, the existence of DNMT3A can be concluded to state the lower life compatibility in Chr2 trisomies than in Chr21 trisomies.

There is a limitation in defining the actual incidence of trisomies because aneuploidies for individual chromosomes cannot be predicted due to undefined abortions. Trisomy 2 is expectedly one of the rarest types of trisomies as well as Trisomy 1. There were

only 3 cases of trisomy 1 reported which all resulted in loss in utero [6]. The length of chromosome 1 is quite similar to Chr2. The largest human chromosome is Chromosome 1 which constitutes 8% of the human genome [7, 8]. Therefore, we also analyzed cell survival and cell death-related protein profiles of Chr1. 48 proteins (8%) and 105 proteins (6%) are involved in cell survival and cell death, respectively. Chr2 has a similar ratio as with each 5% in proliferation and death (Figs. 5B and 3C). Chromosome 21 has been defined as the smallest human autosome representing about 1-1.5% of the human genome [9]. The presence of an extra copy of chromosome 21 is the genetic cause of Down syndrome, which is the most common major cognitive problem affecting 1 in 700 live births. Symptoms frequently observed in most Down syndrome individuals include morphological abnormalities of the head and limbs, short stature, low muscle tone (muscle movement resistance). Other and less frequently observed symptoms are mostly cardiac malformations, gastrointestinal system problems, 20-fold increased risk of leukemia compared to normal individuals, and early onset of Alzheimer's-like neuropathological diseases [10, 11].

CONCLUSION

In conclusion, differences in protein-protein interactions in trisomy 2 and trisomy 21 may help us understand the biological and pathological consequences of these two conditions. While the increased interaction rate in trisomy 2 leads to more complex pathological consequences due to disruptions in cellular functions, the limited interaction network in trisomy 21 may help explain the clinical features of Down syndrome. These studies contribute to our understanding of how molecular differences between the two types of trisomies relate to the biological processes behind the phenotypic differences.

Ethical Statement

Ethical approval is not required for this study. We have used open databases including the websites below:
https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=21%3A1-1000
https://www.ensembl.org/Homo_sapiens/Location/Chromosome?r=2%3A1-1000
https://www.tau.ac.il/~elieis/Housekeeping_genes.html
https://www.geneimprint.com/site/genes-by-species.Homo+sapiens
http://amigo.geneontology.org/amigo
https://www.ensembl.org
https://www.geneimprint.com

Authors' Contribution

Study Conception: EİŞ, SÇU; Study Design: EİŞ, İN, SÇU; Supervision: SÇU; Funding: N/A; Materials: N/A; Data Collection and/or Processing: EİŞ, İN, SÇU; Statistical Analysis and/or Data Interpretation: EİŞ, İN, SÇU; Literature Review: EİŞ, İN, SÇU; Manuscript Preparation: EİŞ, İN, SÇU and Critical Review: EİŞ, İN, SÇU.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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disease ontologies in Down syndrome. PLoS Comput Biol. 2021;17(9):e1009317. doi: 10.1371/journal.pcbi.1009317.
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